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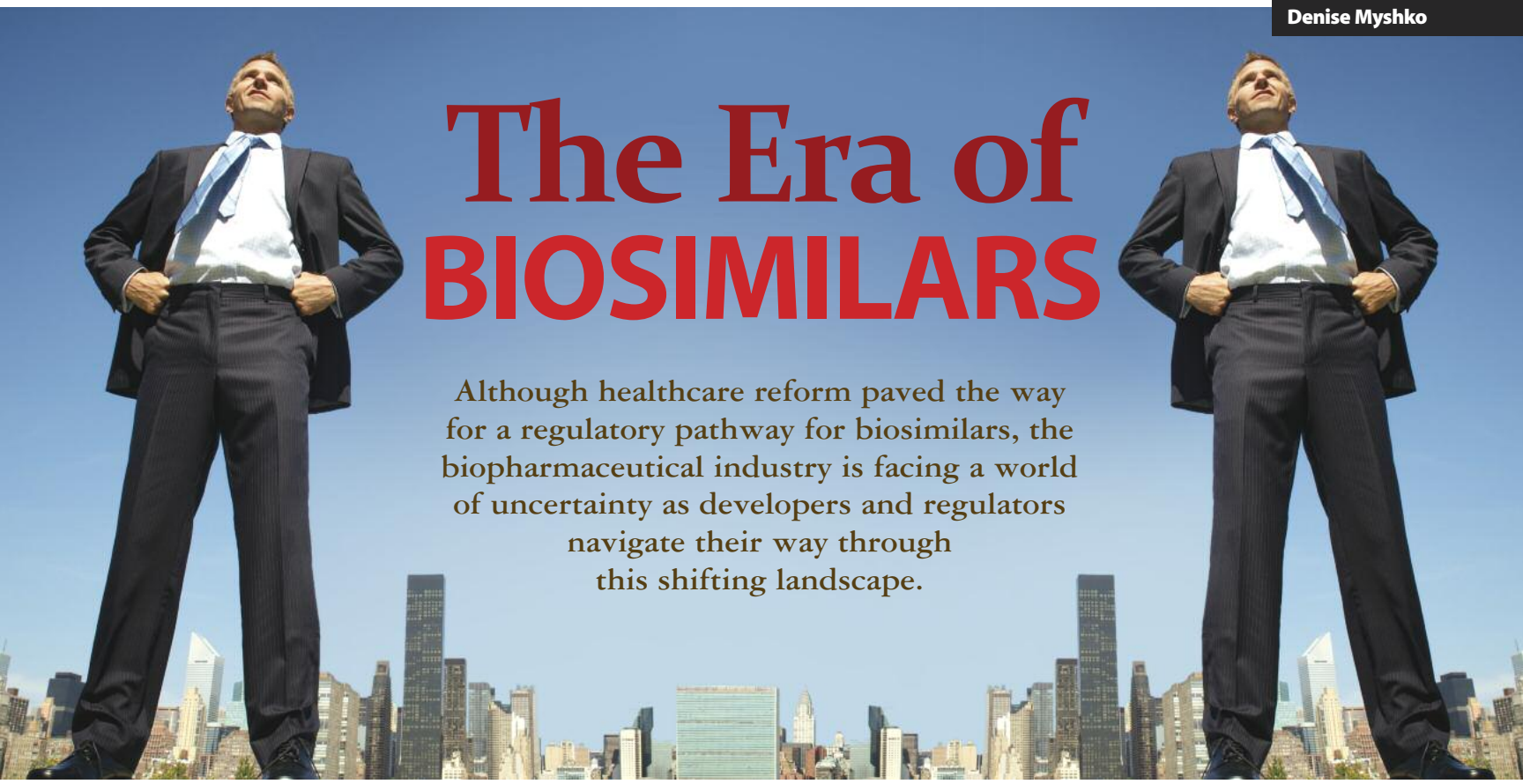


The Era of BIOSIMILARS

Although healthcare reform paved the way for a regulatory pathway for biosimilars, the biopharmaceutical industry is facing a world of uncertainty as developers and regulators navigate their way through this shifting landscape.

Biologics have revolutionized healthcare, helping patients worldwide with serious conditions. More than 200 biologic medicines are available worldwide, and more than 600 new biologic medicines are in development, including treatments for cancer, HIV/AIDS, Alzheimer's disease, and numerous rare conditions.

Now for the first time, new opportunities are presenting themselves for patients and for developers. This is a result of a perfect storm of factors: top-selling biologics will be losing patent protection in the next few years; increasing demand worldwide for lower cost therapies; and new laws and regulations that provide incentives and eventually guidance for the development of biosimilars.

Today, total sales of off-patent biologics amount to about $20 billion, according to Accenture, and this number will increase over the next few years.

Regions outside of the United States — such as Australia, Japan, and the European Union — have approved biosimilar products over the last few years. In the United States, the passage of the Biologics Price Competition and Innovation Act in March 2010 as part of the healthcare reform package provides the FDA with the authority to create a regulatory pathway for biosimilars. The FDA plans to spend $5.7 million in fiscal 2011 to develop drug review standards.

FACT

MORE THAN 30 BRANDED BIOLOGICS WITH SALES OF $51 BILLION ARE SET TO LOSE PATENT EXCLUSIVITY BETWEEN 2011 AND 2015.

Source: Datamonitor

This is a landscape still very much in flux, however. In November 2010, the FDA held a two-day hearing to address the issues and challenges related to the implementation of the biosimilars pathway. FDA officials say they are evaluating comments and submissions resulting from that meeting.

"We are in a period where there is regulatory uncertainty," says Matthew Hudes, national managing principal of biotechnology at Deloitte Consulting. "We know there is a trend toward great emphasis on safety. At the same time, companies have to develop their strategic options in an environment of great uncertainty. Smart companies are investing in areas that give them more flexibility and more options to respond. Companies need to have the greatest amount of flexibility to deal with the changes that are going to come down the line."

Bruce Leicher, senior VP and general counsel at Momenta Pharmaceuticals, points out that developing biosimilars is not like developing generics.

"Right now, a lot of companies have spent their entire history developing drugs through clinical trials," he says. "There are generic companies that have spent their lives copying small molecules. That's not what the biosimilar pathway is about. It's a different business model."

The Biosimilars Market

In 2009, the combined biosimilars market size for the United States and five major European markets was $150 million. With more than 30 branded biologics with sales of $51 billion set to lose patent exclusivity between 2011 and 2015, Datamonitor forecasts that the global biosimilar market will grow from $243 million in 2010 to $3.7 billion in 2015.

Patents for first-generation biologic products, such as erythropoietin (EPO) for the treatment of anemia in those with serious illness, granulocyte colony-stimulating factor (G-CSF) to stimulate white blood cells after chemotherapy, human growth hormone, insulin, and interferon are already expiring.

Decision Resources researchers predict that biosimilar erosion of branded erythropoietin stimulating agent (ESA) market share is likely to be more rapid and more complete in the United States. They also find that oncologists will be the most aggressive in adopting biosimilars compared with other specialties. U.S. oncologists in particular will more rapidly adopt biosimilars compared with their European counterparts.

Generic versions of brand name drugs saved the U.S. healthcare system more than $824 billion over the past decade, and $139.6 billion in 2009 alone, according to a study by IMS Health. The study was commissioned by the Generic Pharmaceutical Association (GPhA) to provide and analyze brand and generic prescription drug sales data for the 10-year period from 2000 to 2009.

The Congressional Budget Office (CBO) estimates that follow-on biologics would initially have prices about 25% below their brand-name counterparts, and after several years of competition prices would be about 40% below the brand name. Biological drugs that will probably face competition from follow-on biologics over the next 10 years currently account for roughly 10% of total drug spending in the United States.

But, CBO officials say, because follow-on biologics may not be viewed as perfect substitutes for their brand-name counterparts — especially when they first become available — sales of those brand name versions will probably continue to represent a large share of total sales through 2019. As a result, CBO estimated that the average reduction in prices across all drugs resulting from the abbreviated approval pathway for follow-on biologics would be about 2% in 2019.

Mr. Hudes agrees that there is going to be less price variation between biosimilars and the brand.

"Biosimilars are going to have much more extensive tests and requirements, as well as a more extensive manufacturing process than generics," he says. "The other question — which is completely unanswered — is the reimbursement side and how biosimilars will be handled, particularly as the government is becoming increasingly the largest payer for prescription drugs."

Mr. Hudes says limited competition will likely influence the pricing of biosimilars as well.

"Competition impacts pricing in the generics area; typically quite a number of companies jump in," he says. "We'll see less of that in biosimilars because of the capital expense and manufacturing expertise that's required. There aren't likely to be a large number of competitors."

This hasn't stopped many large companies from approaching this market. Large pharma companies — including Pfizer, Merck, and Novartis — have expressed commitments to both biologics and biosimilars.

In January 2011, Merck entered into an alliance with Parexel for global clinical development services for designated biosimilar candidates. Merck has disclosed five novel biologics and two biosimilar candidates in clinical development. The company anticipates having five biosimilar programs in late-stage development by 2012.

"Merck has always had a strong tradition in science and this was our opportunity to help shape the science," says Nik Mehta, Ph.D., head of regulatory for biologics at Merck.

The Biosimilars Law

The Biologics Price Competition act was passed as part of the Patient Protection and Affordable Care Act signed by President Obama in March 2010. The law creates an abbreviated approval pathway for biological products and also extends patent protection for FDA-approved biological medicine for 12 years of exclusivity. The law creates two distinct categories of biosimilar products: products that are "biosimilar" to a reference biological product, and products that are "interchangeable" with the reference product.

Dr. Mehta says the biosimilar vs. interchangeable component is a good distinction in the law.

"This is reflective of the fact that biosimilars are not generics," he says. "Interchangeability implies substitution at the pharmacy level. For interchangeability the bar is likely to be much higher at the pharmacy level. It will need to be extraordinarily clear that there are no safety issues related to interchangeability."

Dr. Mehta says Merck will likely approach development with the thought of achieving biosimilar regulatory approval first.

"We are working actively on developing our products, and our scientists are busy working on moving development forward," he says. "At the same time, we are engaging with regulatory authorities in the United States and in Europe about what data will be required to support the approval of our biosimilars."

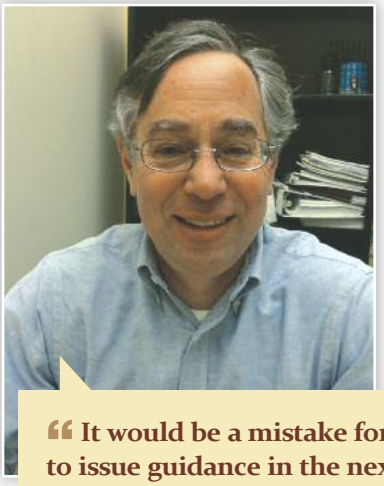
The U.S. law allows for an abbreviated clinical development program for biosimilars, but experts stress this will likely be addressed by regulators on a case-by-case basis, depending on the molecule and the case that can be made for similarity.

"An informed, streamlined development plan for biosimilars is very acceptable," says Bruce Babbitt, Ph.D., principal consultant at Parexel Consulting. "What I mean by 'informed' is that it is already known that the product on the market is safe and effective. The safe dosages, route of administration, as well as the targeted patient populations are known."

Biosimilar Defined

- A "biosimilar" is a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and reference product in terms of the safety, purity, and potency.
- An "interchangeable" is biosimilar to the reference product; it can be expected to produce the same clinical result as the reference product in any given patient; and the risk in terms of safety or diminished efficacy in alternating or switching between use of the biological and reference product is not greater than the risk of using the reference product.

Source: Biologics Price Competition and Innovation Act of 2009



"It would be a mistake for the FDA to issue guidance in the next couple of years because any regulations would be based on academic thinking and not on real products or real data."

BRUCE LEICHER / Momenta Pharmaceuticals

Biosimilars Competitive Landscape

- Short-term competition is likely to come from major generic players. Depending on the regulatory strategies employed by these companies, a trend toward gaining approval through the BLA process instead of a new pathway may be established.
- Big pharma will meet follow-on biologics competition with increased innovation but these companies could also participate in biosimilar development because of available capital and experience.
- In addition to follow-on biologics, big pharma companies will look to develop "me-too" biologics.
- Emerging markets will have more local competition than regulated markets.
- Follow-on biologic manufacturers in emerging markets achieving success domestically will likely compete in the U.S. in the long term.

Source: Thomson Reuters. For more information, visit thomsonreuters.com.

FACT

THE GLOBAL BIOSIMILAR MARKET WILL GROW FROM $243 MILLION IN 2010 TO $3.7 BILLION IN 2015.

Source: Datamonitor

"Unless the data dictate otherwise, designing an informed, streamlined development plan for biosimilars is very acceptable."

DR. BRUCE BABBITT / Parexel Consulting

He says any combination of analytical (in vitro) testing and limited animal testing of the biosimilar candidate head-to-head against the approved reference product provides the necessary information to begin clinical testing.

"For a biosimilar, in most cases companies should be able to proceed directly from Phase I to Phase III trials since Phase II studies are typically required for new biologicals primarily to determine what doses demonstrate efficacy in what patient populations. In other words, since the structural and biological similarity would have already been demonstrated to the reference product, only certain clinical data may be required to confirm similar safety as well as efficacy claims."

Ameet Mallik, global head of biopharmaceuticals at Sandoz, says regulators will look first at how similar the molecule is to the reference product.

"We define the original product as having goal posts, meaning there is normal batch-to-batch variability that exists with the product attributes that can be measured," he says. "We look at the changes and the differences in the product over the course of its lifespan, and this variability sets the goal post for the product. Our goal is to create a biosimilar with product attributes entirely within these goal posts. The more a biosimilar company is able to prove that the product falls within the originator's specifications of normal batch-to-batch variability, the fewer hurdles there are on the clinical side. The more different the product is, the harder it is to prove true biosimilarity on the clinical side."

Sandoz markets three biosimilars: human growth hormone Omnitrope, which was approved in Europe and the United States in 2006 and in Japan in 2009; Binocrit, which was introduced in Europe in 2007 to treat anemia; and Zarzio, which was introduced in Europe in 2009 to stimulate production of white blood cells. The company's sales of biosimilar products were up 63% reaching $185 million in 2010.

Sandoz is developing a biosimilar of rituximab — Roche's Rituxan/MabThera — one of the top three selling biologics worldwide. The company is conducting a Phase II study in patients with rheumatoid arthritis, which aims to demonstrate bioequivalence to the reference product, and is collecting data on pharmacokinetics and pharmacodynamics as well as efficacy and safety.

Mr. Mallik says the interchangeability designation that is possible in the United States doesn't exist in the European regulation.

"The approval pathway in Europe has been around for five years and follows two basic principles," he says. "One is ensuring that the product is comparable, meaning the product itself is essentially the same as the originator and two, ensuring the product is similar through a series of clinical tests. Europe and U.S. laws have addressed two key things: a scientifically justified, abbreviated program, meaning it isn't necessary to duplicate all of the clinical trials that the originator did and once clinical equivalence is demonstrated in one indication, extrapolation to other indications of the originator drug is possible."

Joe Miletich, M.D., Ph.D., senior VP of research and development of Amgen, says the biggest fear about biosimilars is immunogenicity.

"If a biosimilar product has even a minor structural difference, the body might recognize it as a foreign substance and trigger an immune reaction," he says. "And if the biological is highly related to a substance the patient makes naturally, the immune reaction may include that too. This has happened."

For example, Eprex, an anemia drug marketed by Johnson & Johnson outside the United States, was found to result in pure red cell aplasia, a condition in which the bone marrow doesn't make red blood cells. It was determined that a change in the formulation that was initially considered minor led to this increased risk. Patients developed antibodies to the new formulation, which also led to the development of antibodies against the patients' own erythropoietin and other erythropoietin products.

"We can't compromise patient safety," Dr. Miletich says. "We all would prefer that the situation was simpler and that we could come up with a crisp statement of what's required. But it's really not possible to do that without getting into the details of each clinical indication and each biologic. Some of the biologicals are reasonably simple. But others are enormously complex. Biologicals can be different in terms of their complexity by a factor of 10 or more. Therefore, there is no one abbreviated pathway that can apply to all biosimilars."

Dr. Miletich says manufacturing a biosimilar is complex, involving more than the ability to do analytics.

"The entire industry is going through a

learning process," he says. "Over time, we will learn many things. Right now, it's not prudent to assume that minor differences won't matter without clinical data to support that assumption."

Mr. Leicher says the FDA should look at products on a case-by-case basis for some time to come.

"This will give regulators real data to evaluate what works and what doesn't work," he says. "We think it would be detrimental to innovation if the agency were to put into place guidance now."

Mr. Mallik says proving interchangeability, especially, is likely to be a molecule-by-molecule decision.

"The FDA hasn't taken a formal stance," he says. "We believe at least one Phase III clinical trial will be required involving multiple switches between the original product and the biosimilar to prove that the safety, efficacy, and quality of the product is the same and that there are no adverse events for switching between products. The standard for each biosimilar is going to be different."

Challenges and Best Practices

Because of their complexity, cost, and development risks, biosimilar production and commercialization in developed markets are concentrated among only a handful of pharma companies, all of which are established generics players.

Datamonitor experts say despite the introduction of approval pathways in the United States, Europe, and Japan, there remain a large number of barriers to overcome.

Mr. Leicher says the biggest challenge for biosimilars will be process control for manufacturing.

"At every step during the manufacturing process, companies have to make sure the products still fit into the range of variability," he says.

Momenta has developed a set of proprietary tools to unlock what it calls the "black box of biologics manufacturing." Mr. Leicher says the company has spent a lot of time studying the biological mechanisms in cell cultures to help make the proteins.

"We're working to apply our technical platform — where we characterize existing biologics — and then develop the manufacturing process for making biosimilars," he says. "We're focused on biologics that involve glycobiology. Much of our expertise involves understanding the complexity of carbohydrate structures. Monoclonal antibodies, for example, are all glycoproteins."

Dr. Mehta says since the innovator products and manufacturing change over time, it's critical for biosimilar manufacturers to make sure that they develop a broad enough database of product attributes.

"It won't be possible to do just some analytics and put a product on the market," he says. "These models are extraordinarily complicated, and it behooves us to do the development correctly."

Mr. Mallik adds that Europe doesn't take a formulaic approach to biosimilars.

"The outcome depends on how well a company can characterize the biosimilar to the originator — physiochemically, biologically, and functionally — to prove that the molecule is the same," he says. "Companies need to have a clear strategy for their programs. In other words, the programs for each molecule may look different for each company."

Mr. Hudes suggests companies should consider forming alliances and partnering as a way to gain expertise.

"There are lessons that can be learned from participating in an alliance," he says. "Typical generic drug manufacturers could benefit from a partnership. It's an opportunity for big pharma, but I also think specialty pharma companies can take advantage of the opportunity because of the way they are organized. One of the possible trends is having CMOs play a more value-added role in biosimilars, possibly taking more responsibility for product development and providing the process of manufacturing." PV

> **"We support biosimilars coming into the market. But patient safety should not be compromised, and innovation should not be stifled by accepting insufficient protection for what it takes to produce a biologic medicine."**
>
> **DR. JOE MILETICH** / Amgen

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